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## **Functional changes of the reward system underlie blunted response to social gaze in cocaine users**

Preller, Katrin H ; Herdener, Markus ; Schilbach, Leonhard ; Stämpfli, Philipp ; Hulka, Lea M ; Vonmoos, Matthias ; Ingold, Nina ; Vogeley, Kai ; Tobler, Philippe N ; Seifritz, Erich ; Quednow, Boris B

**Abstract:** Social interaction deficits in drug users likely impede treatment, increase the burden of the affected families, and consequently contribute to the high costs for society associated with addiction. Despite its significance, the neural basis of altered social interaction in drug users is currently unknown. Therefore, we investigated basal social gaze behavior in cocaine users by applying behavioral, psychophysiological, and functional brain-imaging methods. In study I, 80 regular cocaine users and 63 healthy controls completed an interactive paradigm in which the participants' gaze was recorded by an eye-tracking device that controlled the gaze of an anthropomorphic virtual character. Valence ratings of different eye-contact conditions revealed that cocaine users show diminished emotional engagement in social interaction, which was also supported by reduced pupil responses. Study II investigated the neural underpinnings of changes in social reward processing observed in study I. Sixteen cocaine users and 16 controls completed a similar interaction paradigm as used in study I while undergoing functional magnetic resonance imaging. In response to social interaction, cocaine users displayed decreased activation of the medial orbitofrontal cortex, a key region of reward processing. Moreover, blunted activation of the medial orbitofrontal cortex was significantly correlated with a decreased social network size, reflecting problems in real-life social behavior because of reduced social reward. In conclusion, basic social interaction deficits in cocaine users as observed here may arise from altered social reward processing. Consequently, these results point to the importance of reinstatement of social reward in the treatment of stimulant addiction.

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# **Social interaction in cocaine users: blunted response to social gaze and underlying functional changes of the reward system**

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## Significance statement

Social interaction deficits in drug users likely impede treatment, increase the burden of the affected families, and consequently contribute to the high costs for the society associated with addiction. However, the neural origin **contributing to** altered social interaction in drug users was unknown so far. The present study illuminates the nature of basic social interaction deficits **as exemplified by social gaze behavior** in cocaine users by applying behavioral, psychophysiological, and functional brain imaging methods. The results suggest that basal social interaction impairments probably arise from blunted social reward processing that was again related to impaired real-life social behavior in cocaine users. These results point to the importance of reinstatement of social reward in the treatment of stimulant addiction.

## Abstract

Social interaction deficits in drug users likely impede treatment, increase the burden of the affected families, and consequently contribute to the high costs for the society associated with addiction. Despite its significance, the neural basis of altered social interaction in drug users is currently unknown. Therefore, we investigated basal social gaze behavior in cocaine users applying behavioral, psychophysiological, and functional brain imaging methods.

In study I, 80 regular cocaine users and 63 healthy controls completed an interactive paradigm in which the participants' gaze was recorded by an eye-tracking device that controlled the gaze of an anthropomorphic virtual character. Valence ratings of different eye-contact conditions revealed that cocaine users show diminished emotional engagement in social interaction, which was also supported by reduced pupil responses. **Study II investigated the neural underpinnings of changes in social reward processing observed in study I.** Sixteen cocaine users and 16 controls completed a similar interaction paradigm as used in study I, while undergoing functional magnetic resonance imaging. In response to social interaction, cocaine users displayed decreased activation of the medial orbitofrontal cortex (mOFC) – a key region of reward processing. Moreover, blunted activation of the mOFC was significantly correlated with a decreased social network size reflecting problems in real-life social behavior because of reduced social reward.

In conclusion, basic social interaction deficits in cocaine users **as observed here may** arise from altered social reward processing. Consequently, these results point to the importance of reinstatement of social reward in the treatment of stimulant addiction.

**Keywords:** *joint attention, reinforcement, OFC, social cognition, joint action, fMRI*

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## Introduction

Cocaine dependence is a chronically relapsing disorder defined by uncontrolled and compulsive drug use (1). Despite severe negative consequences including disrupted social relationships, loss of employment, and somatic and psychiatric illnesses, an addicted person's life is often centered around the drug of choice and activities related to it (2). Therefore, drug use is classified as a major social, legal, and public health problem (3). After cannabis, cocaine is the second most prevalent illegal drug in the United States and Europe (4,5), with a lifetime prevalence among young adults of 6.3% in Europe (15-34 years)(4) and 13.3% in the United States (18-25 years)(6).

Social cognition and social support in drug users are of great clinical relevance, as they have been reported to influence onset of drug use and development of substance use disorders, and treatment success in patients with substance use disorders (7,8). Impairments in social cognition may augment the risk of social isolation, aggression, and depression likely supporting the vicious circle of drug use (9). Additionally, impaired social cognition may contribute to the decay of social relationships in addicted patients (10) with negative consequences for treatment success given that higher social support predicted longer abstinence durations (11). Furthermore, no efficient pharmacological treatment for cocaine addiction is currently available (12), and treatment approaches like cognitive behavioral therapy rely, at least in part, on the emotional responsiveness and social abilities of the drug users (13). Previous results suggest that cocaine users (CU) show impairments in different facets of social cognition, particularly in emotional empathy, mental perspective taking, and emotion recognition in prosody, which are related to deficits in real-life social behavior such as less social contacts and more criminal offences (14,15). Furthermore, in money distribution games, CU act more self-servingly and less altruistically than stimulant-naïve controls (16). Volkow et al. (10) postulated that neuroadaptations in the reward systems of drug users (e.g., ventral striatum and orbitofrontal cortex [OFC]) alter reward processing such that the value of the abused drug is enhanced and concurrently the value of non-drug rewards including social interaction is reduced. Consequently, general social competence might become impaired and promote antisocial and criminal behavior. This may explain why social consequences of drug use (e.g., imprisonment or familial problems) do not prompt drug addicted people to quit using the drug and how they contribute to increased drug use and transition from recreational drug use to addiction (10). However, while altered processing of monetary

rewards has been reported in CU (17,18), social reward processing has not been studied yet - neither on the psychological nor the neural level. Therefore, it remains elusive if CU i) show behavioral differences to reward stemming from social interactions, and if so ii) which neural adaptations within reward circuitry underlie these potential changes in social interaction behavior.

An essential part of social interaction is the phenomenon of “social gaze”, which has two aspects: Gaze can be used by the gazing person as a deictic cue to manipulate the attention of others and can be read out by observers as a hint towards attentional focus of the gazing person (19). Both aspects can converge in joint attention (JA), which is a central element of social interaction (20) and is established when a person follows the direction of another person’s gaze so that both attend to the same object (21). Engagement in JA is considered to reflect our understanding of another person’s point of view (22,23). The capacity of JA emerges at 8 to 12 months of age (24) and is predictive for later language learning (25) and the development of more advanced social skills such as mental perspective taking (e.g., the attribution of intentions and goals to others, also known as *Theory-of-Mind*)(26). Impaired JA is a core symptom of autism spectrum disorders (27).

To test for social **gaze** differences between CU and healthy controls (CU) we applied a paradigm designed to capture the reciprocal and interactive nature of JA (28)(**Figure S1**), where participants engage in an online interaction with an anthropomorphic virtual character in real-time. Compared to self-initiated nonjoint attention (NJA, i.e. if the counterpart does not follow one's gaze but rather pays attention to another object) self-initiated JA (i.e. if the counterpart follows one's own gaze) is perceived as more pleasurable and associated with stronger activation of reward-related brain areas in healthy controls (HC)(28). This rewarding nature of JA might underlie the human motivation to engage in the sharing of experiences that emerges in early childhood (25,28).

It has been suggested that changes in social reward processing might underlie alterations in social behavior and cognition in CU (10). Here, we conducted two studies assessing JA processing, **which constitutes an elegant approach to investigate basic social interaction patterns related to social reward processing** (28), in CU and stimulant-naïve HC by means of behavioral, psychophysiological, and functional brain imaging methods. In study I, a large sample of relatively pure CU with few psychiatric comorbidities (n=80) and stimulant-naïve HC (n=63) completed an interactive JA task (28), while valence and arousal ratings, error scores, reaction time, and pupil size were obtained. Pupil dilation provides an objective index of affective processing (29,30). Based on the observations

obtained in study I, we further investigated the neural correlates of the blunted emotional response to social gaze in subsamples of 16 CU and 16 HC employing functional magnetic resonance imaging (fMRI) during an abridged version of the paradigm (study II). We hypothesized that altered emotional responses to JA is accompanied by less pronounced activation in reward-related brain areas of CU.

## Results

### *Demographic characteristics*

In study I and II, CU and HC did not differ with respect to verbal intelligence quotient (IQ), years of education, sex distribution, smoking status, and age (**Table 1**). As expected, CU scored significantly higher than HC in the Beck Depression Inventory (BDI) and Fagerström Test of Nicotine Dependence (FTND) sum score in study I. Furthermore, HC reported a significantly larger social network than CU in study I, as shown in this sample before (14). Self-reported drug use, urine toxicology status, and results of 6-month quantitative hair toxicologies are displayed in the **Table S1** (study I) and **Table S2** (study II).

### *Study I*

A mixed-effects ANOVA [group(HC vs. CU)\*initiation (self vs. other vs. object)\* joint(JA vs. NJA)] performed for valence ratings yielded a significant main effect for the factor joint ( $F(1,141)=10.17$ ,  $p<0.01$ ) and a significant group\*joint interaction ( $F(1,141)=4.35$ ,  $p<0.04$ ), indicating that both groups rated JA trials as more pleasant than NJA trials but that CU differentiated less between JA and NJA trials than HC (**Figure 1A**). The main effects for group and initiation, and the group\*initiation interaction did not reach statistical significance (all  $p>0.09$ ).

For the arousal ratings a mixed-effects ANOVA revealed a significant group\*joint interaction ( $F(1,141)=3.94$ ,  $p<0.05$ ) (**Figure 1B**), indicating that HC rated the JA trials as less arousing than NJA trials, while CU showed the reversed pattern. Furthermore, a significant main effect was found for the factor initiation ( $F(2,282)=18.06$ ,  $p<0.001$ ) (**Figure S2**), suggesting that both groups rated self-initiated trials as the least arousing condition, while the other-initiated condition was experienced as the most arousing initiation condition. The main effects for group and joint, and the group\*initiation interaction did not reveal significant differences (all  $p>0.38$ ).

A mixed-effects ANOVA performed for pupil size yielded a significant main effect for the factor joint ( $F(1,130)=185.02$ ,  $p<0.001$ ), suggesting increased pupil dilatation during NJA trials compared to JA



trials in both groups. A significant group\*joint interaction ( $F(1,130)=4.91$ ,  $p<0.03$ ) was revealed, indicating that the change in pupil size between JA and NJA trials was larger in HC than in CU (**Figure 1C**). This corroborates the results obtained for the valence ratings (see above). The main effects for group and initiation, and the group\*initiation interaction did not reach statistical significance (all  $p>0.16$ ). Thus, pupil size data suggest a processing pattern of JA similar to valence ratings: both measures reveal that CU process JA differently from HC. More precisely, CU do not differentiate to the same degree between JA and NJA as HC do.

The number of errors (looking at the wrong object in the other and object initiation condition), number of completed trials, and reaction times did not differ between groups (all  $p>0.28$ ) and did not reveal a significant group\*joint interaction (all  $p<0.09$ ) (**Table S3**), suggesting that HC and CU did not show global performance differences in the task.

These results suggest an altered emotional involvement in social gaze interaction in CU. As social gaze processing has previously been linked to the reward system (28), we further investigated in study II whether the changed social interaction of CU can be explained by altered activation of reward areas.

## *Study II*

Valence and arousal ratings obtained during fMRI replicated the results of study I, although the main effects and interactions did not reach significance most likely due to the small sample size (**Figure S3**).

Results of the region-of-interest (ROI) analyses for one-sample (HC) and between group (HC>CU) tests are displayed in **Table S4**. We focused on five ROIs (medial orbitofrontal cortex (mOFC), ventral striatum, left posterior hippocampus, medial prefrontal cortex (mPFC), and posterior cingulate cortex (PCC)). These regions were chosen because they are established core structures of the reward system (for details see **Methods section**). Significantly stronger activation for self-initiated JA>self-initiated NJA was found in three of the five ROIs in the control group: mOFC, mPFC, and PCC (**Figure S4 and Table S4**). This is in-line with the notion that JA is more rewarding than NJA. In the group contrast, CU displayed significantly less pronounced activations of the mOFC during self-

initiated JA>self-initiated NJA as compared to HC (**Figure 2A&B and Table S4**). No significant differences in activation were found for the inverse contrast and any other condition.

A correlation analysis was conducted to investigate the association between blood oxygen level dependent (BOLD) responses in the mOFC to self-initiated JA>self-initiated NJA and social network size. If the mOFC activation is related to value of social reward, then there should be a relation to social network size as an indicator of real-life social behavior. To test this prediction, uncontaminated by the already determined difference in social network size between the two groups, we assessed it only in HC. A significant positive correlation was found in the mOFC (peak:  $x=-12$ ,  $y=50$ ,  $z=-5$ ,  $p<0.05$ , FWE), indicating that lower mOFC activity in response to JA>NJA was associated with a smaller size of the social network a person has. **Figure 2C** displays the correlation of social network size and the first eigenvariate of the mOFC ROI for HC ( $r=0.49$ ,  $p<0.05$ ). This correlation was also significant in the total sample ( $r=0.35$ ,  $p<0.05$ ) but not in CU alone ( $r=0.16$ ,  $p=0.56$ ). **Correlation coefficients did not differ significantly ( $z=0.99$ ,  $p=0.32$ ) between CU and HC. Furthermore, valence ratings of study I were significantly correlated with pupil size of study I ( $r=-0.39$ ,  $p<0.05$ ) and additionally also with mOFC activation in study II ( $r=0.36$ ,  $p<0.05$ ) in response to JA vs. NJA.**

## Discussion

The present study demonstrates that CU process social gaze (“joint attention”, JA) differently than HC, and that these impairments are related to a reduced activation of the brain’s reward system in situations of social interactions. To our knowledge, the present study represents the first experimental and multimodal investigation of **basic** social interaction behavior and its relation to social reward processing in CU.

The analysis of valence ratings revealed that HC clearly rated JA as more pleasant than NJA, while CU differentiated less between both conditions. All participants rated the self-initiated JA condition as the most pleasant, while self-initiated NJA was perceived as the least pleasant condition (**Figure S5**), which is in accordance with Schilbach et al (28). Furthermore, arousal ratings showed that CU feel more aroused by JA trials, while HC rated NJA as more arousing. This demonstrates for the first time that emotional involvement and processing of social gaze is altered in CU. Note that these results cannot be attributed to differences in attention, motivation, or the ability to complete the task, as groups did not differ in the number of errors, the number of completed trials and reaction times.

Providing objective data, also reduced reactivity of pupil size supports the assumption that emotional engagement by social eye contact is altered in CU: In agreement with valence ratings, the difference in pupil size between JA and NJA was significantly smaller in CU than HC. Pupil size is considered a physiological marker of affective engagement and is highly correlated with other indices of autonomic responsiveness such as skin conductance (31,32). Pupil changes during the processing of emotionally engaging stimuli are mediated by increased sympathetic activity which in turn increases activity of the dilator muscle (32). Moreover, pupil responses are sensitive to abnormal social reward and social threat processing in children with autism spectrum disorders (33). The reduced pupil response in CU may thus reflect reduced sensitivity of CU to the differential emotional value of JA and NJA, and altered autonomous processing of social information. This reduced sensitivity might be a result of blunted social reward processing, as JA processing has been shown to involve reward-related brain areas (28).

It has been hypothesized that impairments in social cognition in drug users arise from an altered reward system by assigning more value to the drug but less value to natural reinforcers (10). The present results test this hypothesis into the social domain and extend previous reports of deficits in social cognition of CU (14,34-37). Indeed, basal social mechanisms such as JA abilities had not been investigated in drug users so far. Difficulties at this basic level of social interaction might represent an underlying mechanism which could help explain impairments in more sophisticated social skills (26), as the pupil response to JA was correlated with mentalizing ability ( $r=0.29$ ,  $p<.001$ ,  $N=132$ ) as measured with the *Movie for the Assessment of Social Cognition* (MASC) in the presently studied sample as previously described (14).

Furthermore, JA seems to have a stronger arousing effect than NJA trials in CU. This might indicate that CU – unlike controls – perceive gaze contact as socially threatening or as an intrusion of personal space inducing fear or aggression, which is often associated with increased arousal (38,39). CU probably display increased sensitivity to social dominance as previous studies in monkeys showed that cocaine acted as a reinforcer mainly in subordinate but not in dominant monkeys (40). However, this speculation should be tested in future studies.

As the neural basis of altered social interaction in drug users has not been investigated yet, study II was conducted to investigate the involvement of the reward system during social gaze processing in CU and HC using fMRI. Corroborating previous findings of studies investigating JA and social cognition (28,41,42), we initially demonstrated that self-initiated JA vs. NJA recruited several reward-related areas (mPFC, mOFC, and PCC) in our control participants. These areas have repeatedly been shown to be associated with social cognition (43). Importantly, CU showed significant less activation of the mOFC in response to self-initiated JA vs. NJA compared to control participants. This is in accordance with previous studies reporting functional and structural alterations in the OFC in CU (44,45). Numerous studies provide evidence that the mOFC plays a critical role in reward-guided behavior and emotion processing. More specifically, the mOFC has been shown to be associated with encoding and maintenance of stimulus-reward value of primary and secondary reinforcers (46-48) and seems to be critically involved in emotional learning (49). As part of the reward system, the mOFC predominantly projects to the ventral striatum (47,50) and both areas have been shown to be altered in

function in CU (51-53). Consequently, decreased mOFC activation in CU in response to JA likely indicates altered social reward processing and may underlie social deficits in CU. Significant correlations between mOFC activation, pupil size, and valence ratings further corroborate the assumption of a common underlying process.

Besides reward processing, the mOFC is also involved in other cognitive functions such as impulse control and decision-making supposed to be impaired in cocaine users (53-55). However, behavioral impulsivity as measured with the Stop-Signal Task in the current sample (previously described in detail: 56) were not correlated with mOFC activation in controls, CU, or the complete sample (all parameters  $p > 0.11$ ). Therefore, differences in impulse control are unlikely to account for the mOFC hypoactivation during JA processing in CU. However, further studies are necessary to investigate the influence of other factors.

Correlation analyses may provide further evidence for a relationship between mOFC activation and real-life social functioning given that a stronger activation of this region during self-initiated JA vs. NJA was associated with a larger social network size in HC. Even though correlation coefficients did not differ significantly between groups, the correlation between mOFC activation and social network size was not significant in CU alone. These findings support the assumption that JA could represent a fundamental mechanism of social cognition, which has implications for more complex social abilities (26). Consequently, altered social reward processing in CU may impact real-life social behavior, such as social withdrawal or social rejection. This can be particularly important, as social environment and behavior are crucial factors in the onset of drug use as well as for the outcome of drug addiction treatment (7,8). Moreover, enhanced OFC activity in CU in response to drug-related words has been associated with increased reward valuation for drug cues (57). In conjunction with the current results, this supports the assumption that neuroadaptations in brain reward systems make drug users more sensitive to the abused drug and may reduce responsiveness to the value of non-drug reinforcers such as social interaction (10). Altered reward sensitivity might therefore reduce the motivation to engage in social interaction, decrease the possibilities to learn and apply social skills, and promote antisocial behavior. This might result in impairments in general social competence and might explain why even

substantial negative social consequences such as legal or family problems do not bring the addicted person to give up drug use.

The present study has to be interpreted with the following limitations in mind: While the sample size in study I was large, only a relatively modest subsample could be included in study II. Therefore, due to limited power we might not have been able to detect differential activations in other reward-related brain areas such as the ventral striatum. Furthermore, to obtain greater experimental control, the participants were interacting with an avatar instead of a real human being. Note though that participants who did not believe that the avatar was controlled by another human were excluded from study I and not invited to study II. In addition, previous investigations demonstrate that using avatars is an adequate tool to study the processing of face-based social stimuli (28,58). **Moreover, although JA processing represents an elegant tool to investigate basic social interaction behavior as represented by gaze contact, it cannot cover all facets of social interaction behavior. Even though the correlation of mOFC activation and social network size may indicate that altered processing of social gaze in cocaine users is related to real-life differences in interaction behavior, it is possible that other factors such as personality traits or economical status also contribute to differences in social network size.** Finally, due to the cross-sectional design, we cannot exclude that social impairments have preceded cocaine use and possibly represent a vulnerability to start using drugs. Importantly, comprehensive psychiatric diagnostics and objective characterization of drug use by hair toxicology suggest that our CU showed little psychiatric co-morbidities and relatively sparse polytoxic drug use.

In sum, our study provides first-time evidence of impairments of basal social interaction behavior as reflected by changes of social gaze behavior in CU, and suggesting a link between these impairments and altered social reward processing both on the behavioral and neural level. Social cognition and interaction deficits in cocaine users are a relevant problem for the social environment and treatment success of affected individuals and by extension for society at large (3,7). Understanding the basis of social cognition deficits in stimulant users offers the possibility to develop new targets for prevention and treatment strategies. Trainings of social reward and social reward processing might be beneficial to abate harm caused by altered social processing in substance use disorders.

## Materials and Methods

### *Participants*

For study I 80 CU and 63 stimulant drug-naïve control participants were included, while a subpopulation of 16 CU and 16 HC participated in study II (for recruitment details see **SI Text**). Inclusion criteria for the cocaine using group was cocaine use of at least 1g per month, cocaine as primary used illegal drug, and a current abstinence duration of no longer than 6 months. Exclusion criteria for the CU were use of opioids, a polytoxic drug use pattern, and axis I DSM-IV adult psychiatric disorders other than cocaine, nicotine, and alcohol abuse/dependence, history of depression, and ADHD due to their high prevalence in CU. Exclusion criteria for control subjects were any axis-I DSM-IV psychiatric disorder with exception of nicotine dependence, and regular illegal drug use (lifetime use <15 occasions) with exception of occasional cannabis use. For both groups, exclusion criteria were clinically significant somatic diseases, head injury or neurological disorders, family history of schizophrenia or bipolar disorder, and use of prescription drugs affecting the CNS. Participants were asked to abstain from illegal substances for a minimum of three days and from alcohol for at least 24h. Self-reports were controlled by urine toxicology and 6-month-hair (for details see 14,59). Additionally, for study II participants had to be right-handed as confirmed by the Edinburgh Handedness Questionnaire (60) and fulfill MRI safety criteria. All participants had normal or corrected to normal vision. The studies were approved by the Cantonal Ethics Committee of Zurich (KEK). All participants provided written informed-consent statements in accordance with the declaration of Helsinki and were compensated for their participation.

### *Procedure*

The present data were collected in the context of the Zurich Cocaine Cognition Study (ZuCo<sup>2</sup>St) (14,16,59,61). A Structured Clinical Interview for axis-I DSM-IV Disorders (SCID-I) was carried out by a trained psychologist. Drug use data were collected by means of the Interview for Psychotropic Drug Consumption (62). The brief version of the Cocaine Craving Questionnaire (CCQ)(63) was applied to assess current cocaine craving. Smoking habits were captured with the FTND (64). The

Mehrfachwahl-Wortschatz-Intelligenztest (MWT-B)(65), a standardized German vocabulary test, was carried out for the estimation of premorbid verbal IQ. The BDI (66) was used to assess current depression symptoms. The Social Network Questionnaire (SNQ)(67) was applied to measure individual social network size (for details see 14). In study I, participants completed the test described below together with a neuropsychological test battery (14,16,59,61). Study II took place on a separate day.

### *Social Gaze Task*

The interactive social gaze task was based on the test described in previous publications (28,68). In brief, the participant's gaze was recorded by an eye-tracking device and used to control the gaze of an anthropomorphic virtual character (avatar). The participants completed three initiation conditions: 1) leading the gaze of the avatar (*self* condition), 2) following the gaze of the avatar (*other* condition), 3) the direction of the gaze was determined by a third object (*object* condition). In every initiation condition the participant either looked in the same direction as the avatar (JA) or in another direction (NJA). For details see **SI Text**.

### *Eye-tracking*

In study I gaze directions were recorded using the Eyelink 1000 system (SR Research Ltd, Canada), while in study II, an MRI compliant eye-tracking system including video goggles (Resonance Technology, USA) was used. The systems produced real-time output of gaze positions, which was transferred via a fast network connection to another computer controlling the visual stimulation. For technical details and pupil size analysis please see **SI Text**.

### *Image Acquisition and Preprocessing*

Magnetic resonance images were acquired on a Philips Achieva 3.0T whole-body scanner (Best, The Netherlands) equipped with a 32-channel receive head coil and MultiTransmit parallel RF



transmission. Functional (fMRI) data were acquired using a whole brain gradient-echo EPI sequence (TR=2500ms, TE=35ms, slice thickness 3mm, 40 axial slices, no slice gap, field of view 240x240mm<sup>2</sup>, in-plane resolution 3x3mm, SENSE reduction factor 2.0). Additionally, high-resolution anatomical images (voxel size=1x1x1mm) were acquired using a standard T1-weighted 3-D MP-RAGE sequence.

Images were analyzed using SPM8 ([www.fil.ion.ucl.ac.uk/spm](http://www.fil.ion.ucl.ac.uk/spm)). Preprocessing consisted of realignment, spatial normalization to the standard EPI template of the Montreal Neurological Institute (MNI), and spatial smoothing using a Gaussian kernel of 6mm FWHM to meet the statistical requirements of the general linear model (GLM).

### *Statistical Analysis*

Study I: frequency data were analyzed by means of Pearson's Chi-square test and quantitative data by mixed-effects analyses of variance (ANOVA) using PASW 18.0 (IBM, Switzerland). In all ANOVAs, group (CU vs. HC) was introduced as between-subjects factor, while initiation (self, other, object) and joint (joint vs. nonjoint trials) were introduced as within-subjects factors. The confirmatory statistical comparisons of all data were carried out on a significance level set at  $p < .05$  (two-tailed).

Study II: the fMRI images were analyzed using a GLM as implemented in SPM8. The experimental conditions (self-initiated JA, self-initiated NJA, other-initiated JA, other-initiated NJA, baseline) were modeled as 5s blocks convolved with a canonical hemodynamic response function in the first-level analysis for each subject. Trials without a successful object fixation were modeled using a separate regressor of no interest. Low-frequency signal drifts were filtered using a 128s high-pass filter. The following contrasts were computed for each participant: 1) JA>NJA 2) self-initiated JA> self-initiated NJA 3) other-initiated JA>other-initiated NJA. The individual contrasts were then entered into a second-level group analysis using a between-group two sample t-test for the comparison between CU and HC, and a one sample t-test for the analysis within the control group with a threshold of uncorrected  $p < 0.005$ . Group effects were then analyzed using small volume correction (SVC). As we were particularly interested in reward related areas and due to the a priori hypothesis, five ROIs were

defined based on previous identification of areas associated with immediate reward processing (69): mOFC, ventral striatum, left posterior hippocampus, mPFC, PCC. Search volumes were defined as spheres with a 5mm radius centered on previously reported MNI coordinates (59). These volumes were applied to the one-sample t-test in the control group, the two-sample t-test to compare CU and HC, and the correlation analysis investigating the relationship between brain activation for the self-initiated JA>self-initiated NJA contrast and social network size as an indicator of real-life social behavior. Family-wise error (FWE) corrections were used in all SVC ROI analyses at a threshold of  $p < 0.05$ .

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## Figure Legends

**Figure 1** – Mean difference in valence ratings (A) and in arousal ratings (B) for joint vs. nonjoint attention trials for controls (n=60) and cocaine users (n=83), and mean pupil size difference between joint attention and nonjoint attention trials for controls (n=60) and cocaine users (n=72). Error bars refer to SEM. \*indicates significant difference at  $p < .05$ .

**Figure 2** – Between group activation (controls [n=16] > cocaine users [n=16]) for the self-initiated joint attention > self-initiated nonjoint attention contrast (displayed at uncorrected  $p < 0.01$ )(A) and corresponding contrast estimates in the mOFC (B). Positive association between social network size and mOFC activation for the self-initiated joint attention > self-initiated nonjoint attention contrast in controls ( $r = 0.49$ ,  $p < 0.05$ , 1<sup>st</sup> eigenvariate)(C).

**Table 1** Demographic data (means and standard deviation)

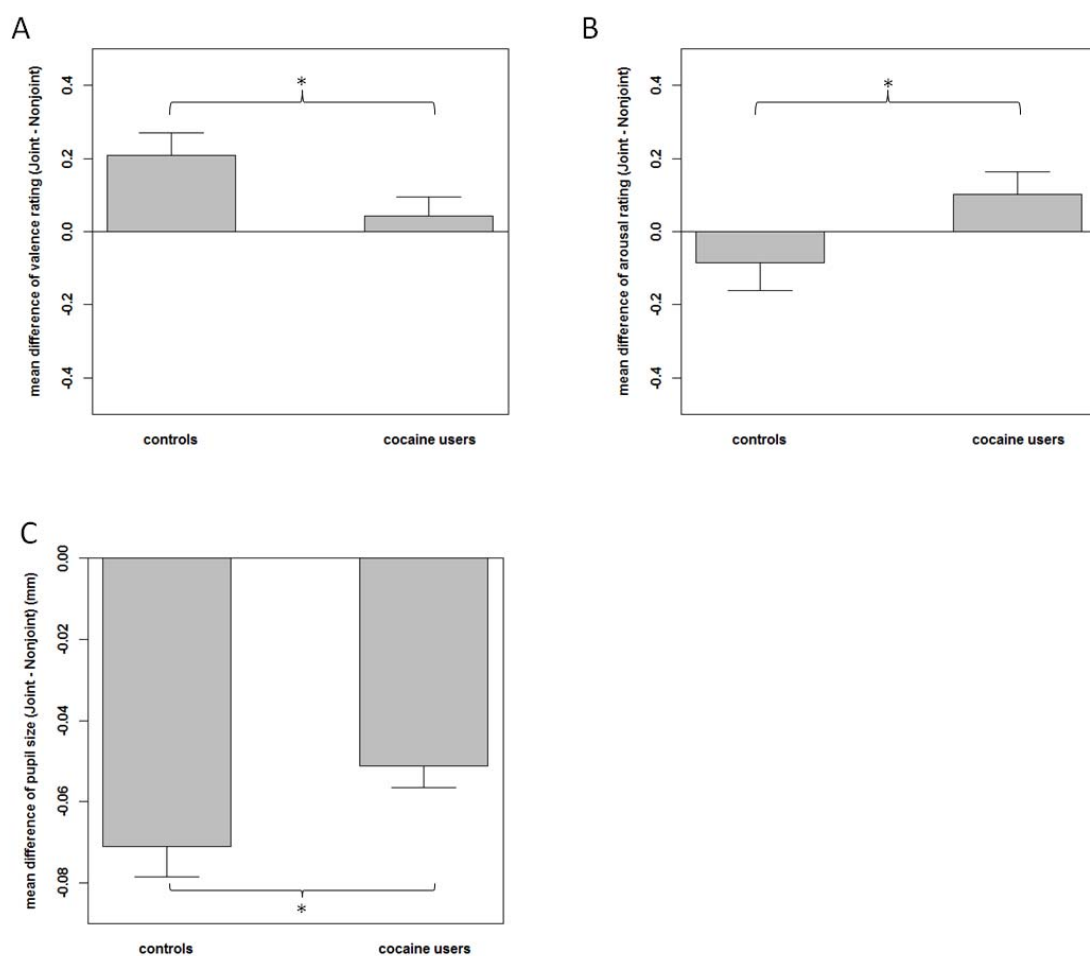
		Control group (n=63)	Cocaine users (n=80)	Value	df	p
Study I	Male/female participants (n)	42/21	59/21	$\chi^2 = 0.85^b$	1	0.36
	Age	29.65 (8.95)	30.06 (9.00)	$T = -0.27^a$	141	0.79
	Years of education	10.51 (1.74)	10.07 (1.73)	$T = 1.50^a$	141	0.14
	Verbal IQ	105.22 (9.99)	102.74 (11.22)	$T = 1.38^a$	141	0.17
	Smoker/nonsmoker (n)	46/17	64/16	$\chi^2 = 0.97^b$	1	0.33
	FTND sum score (0-10) <sup>c</sup>	2.46 (2.20)	3.85 (2.43)	$T = -3.10^a$	110	<b>&lt;0.01</b>
	BDI sum score (0-63)	4.06 (3.89)	9.36 (7.91)	$T = -4.90^a$	141	<b>&lt;0.001</b>
	Social network size (SNQ)	26.41 (13.19) (n=60)	19.94 (12.05) (n=72)	$T = 2.94^a$	130	<b>&lt;0.01</b>
		Control group (n=16)	Cocaine users (n=16)	Value	df	p
Study II	Male/female participants (n)	12/4	12/4	$\chi^2 = 0.00^b$	1	1.00
	Age	32.63 (8.33)	33.38 (9.12)	$T = -0.24^a$	30	0.81
	Years of education	11.25 (1.61)	11.00 (1.51)	$T = 0.45^a$	30	0.65
	Verbal IQ	106.63 (11.16)	104.56 (10.62)	$T = 0.54^a$	30	0.60
	Smoker/nonsmoker (n)	9/7	11/5	$\chi^2 = 0.53^b$	1	0.47
	FTND sum score (0-10) <sup>c</sup>	1.63 (1.85)	4.40 (3.63)	$T = -1.96^a$	16	0.07
	BDI sum score (0-63)	2.63 (2.53)	6.94 (8.63)	$T = -1.92^a$	30	0.07
	SNQ total network size	24.88 (14.39)	20.20 (13.43) (n=15)	$T = 0.93^a$	29	0.36

Significant *p* values are shown in bold. Means and standard deviation of means in parenthesis.

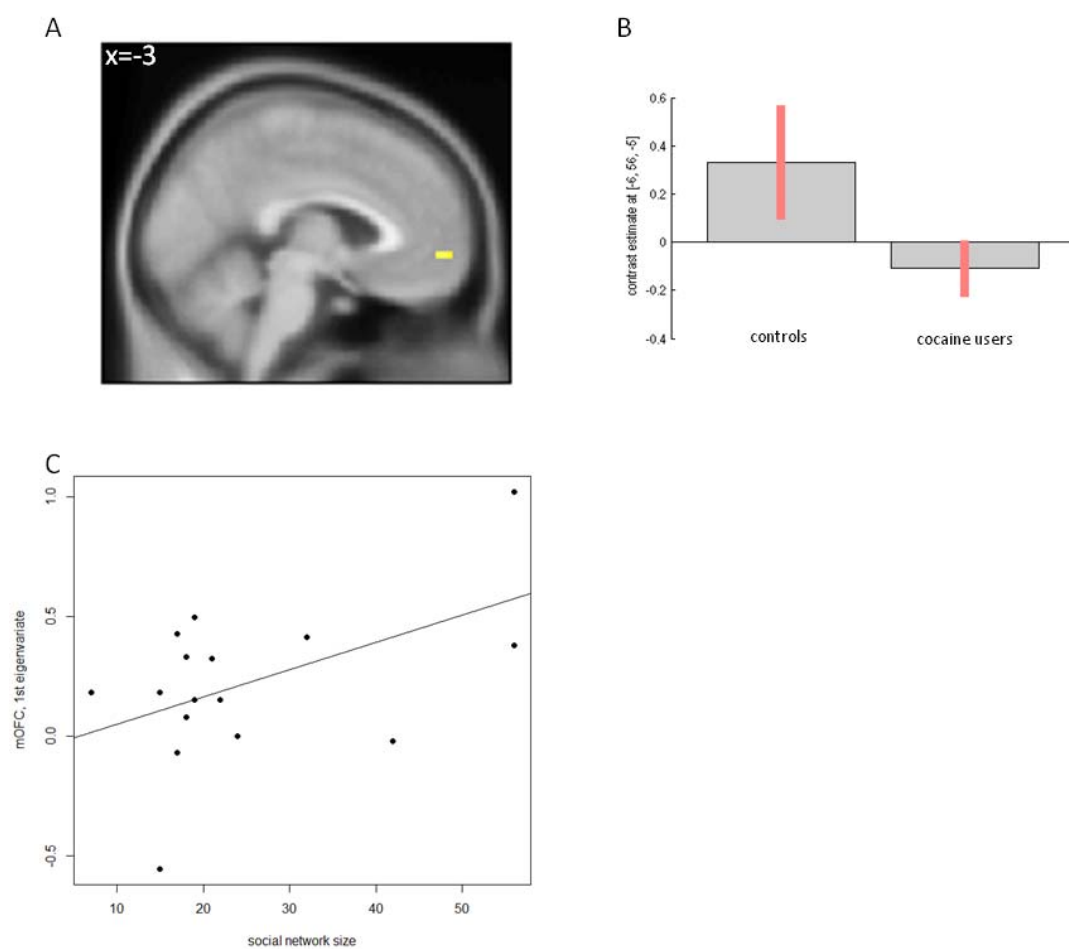
FTND, Fagerstrom Test of Nicotine Dependence (in smokers only); BDI, Beck Depression Inventory; SNQ, Social Network Questionnaire

<sup>a</sup>Independent T-Test, <sup>b</sup> $\chi^2$  test (across all groups) for frequency data, <sup>c</sup>FTND measured in smokers only



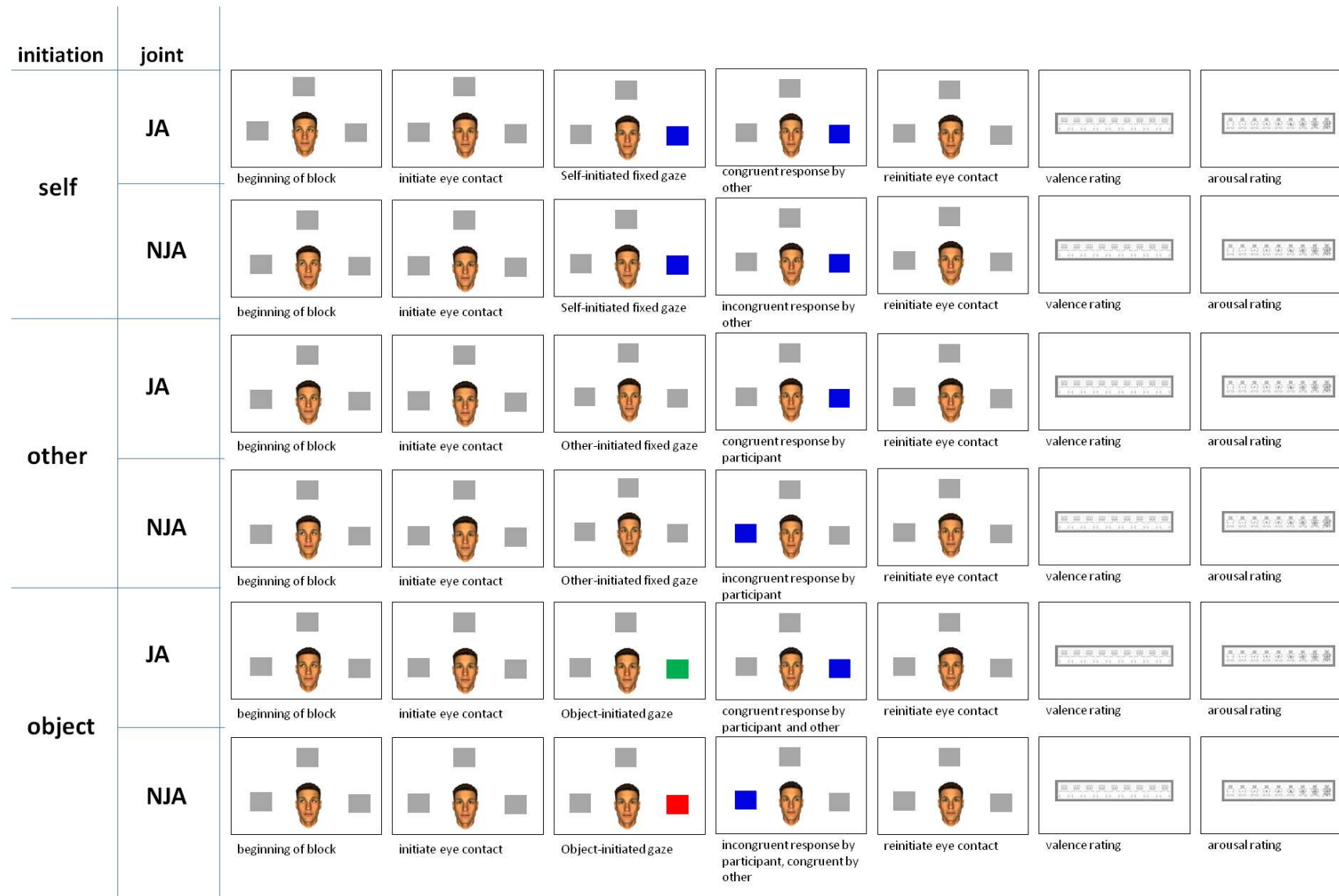


**Fig. 1**



**Fig. 2**

## Supplementary Information



**Figure S1** – Design of the social gaze paradigm in study I.

**Table S1** Study I: Pattern and amount of drug use, urine toxicology, and hair samples

	Control group (n=63)	Cocaine users (n=80)
<i>Cocaine</i>		
times per week	-	1.76 (1.87)
grams/week	-	3.56 (10.13)
years of use	-	6.89 (5.00)
maximum dose (24h)	-	5.69 (6.34)
last consumption (days)	-	25.29 (36.51)
cumulative dose (grams)	-	2203.96 (6127.96)
urine toxicology (pos/neg)	-	18/62
craving for cocaine (0-70)	-	20.55 (10.54)
hair sample (pg/mg)		
Cocaine	-	9880.94 (22237.28)
Benzoyllecgonine	-	2239.31 (5218.92)
Ethylcocaine	-	930.17 (2382.70)
Norcocaine	-	267.51 (533.33)
<i>MDMA</i>		
tablets/week	-	0.21 (1.14)
years of use	1.58 (11.49)	2.60 (4.40)
last consumption (days)	-	97.46(144.45) (n=25)
cumulative dose (tablets)	0.83 (3.00)	72.82 (251.33)
hair sample (pg/mg)	2.88 (16.64)	487.54 (1461.10)
<i>Cannabis</i>		
grams/week	0.62 (1.56)	1.03 (2.73)
years of use	4.18 (5.02)	8.76 (7.41)
last consumption (days)	33.56 (48.85) (n=29)	40.19 (126.56) (n=53)
cumulative dose (grams)	328.76 (665.88)	1988.92 (4035.33)
urine toxicology (pos/neg)	9/54	18/62
<i>Amphetamine</i>		
grams/week	-	0.07 (0.21)
years of use	0.01 (0.06)	1.31 (2.64)
last consumption (days)	-	86.95 (143.19) (n=26)
cumulative dose (grams)	0.20 (1.48)	20.43 (59.75)
hair sample (pg/mg)	-	74.50 (244.26)
<i>GHB</i>		
cumulative dose (pipettes)	-	1.83 (8.87)
<i>Hallucinogenes</i>		
cumulative dose (times)	1.53 (7.15)	5.41 (9.59)
<i>Alcohol</i>		
grams/week	116.76 (129.45)	179.76 (180.80)
years of use	12.75 (9.06)	11.69 (6.93)
<i>Nicotine</i>		
cigarettes per day	8.97 (9.98)	13.52 (9.64)
years of use	8.60 (9.24)	11.08 (8.16)

Means and standard deviation of means in parenthesis

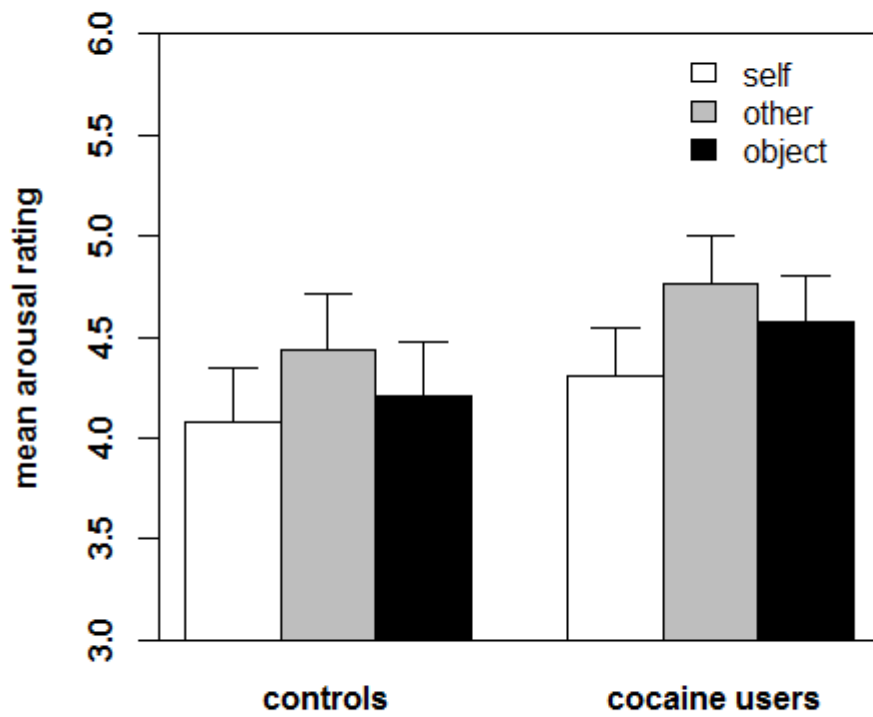
Consumption per week, duration of use, and cumulative dose are averaged within the total group. Last consumption is averaged only for persons who used the drug in the last 6 months. In this case, sample size (n) is shown.

**Table S2** Study II: Pattern and amount of drug use, urine toxicology, and hair samples

	Control group (n=16)	Cocaine users (n=16)
<i>Cocaine</i>		
times per week	-	0.75 (0.84)
grams/week	-	1.01 (1.2)
years of use	-	8.8 (6.11)
maximum dose (24h)	-	3.02 (1.49)
last consumption (days)	-	17.30 (16.90)
cumulative dose (grams)	-	708.15 (842.78)
urine toxicology (pos/neg)	-	10/6
craving for cocaine	-	20.25 (12.81)
hair sample (pg/mg)		
Cocaine	-	8241.56 (14016.86)
Benzoylecgonine	-	1698.12 (2817.41)
Ethylcocaine	-	447.81 (953.80)
Norcocaine	-	245.47 (502.44)
<i>MDMA</i>		
tablets/week	-	0.06 (0.22)
years of use	0.25 (1.00)	2.25 (3.31)
last consumption (days)	-	100.42 (n=1)
cumulative dose (tablets)	0.69 (2.50)	15.82 (24.90)
hair sample (pg/mg)	-	32.13 (75.98)
<i>Cannabis</i>		
grams/week	0.01 (0.02)	0.62 (1.53)
years of use	1.34 (1.60)	10.94 (9.95)
last consumption (days)	109.60 (113.73) (n=4)	13.40 (22.15) (n=6)
cumulative dose (grams)	33.70 (71.10)	590.42 (1071.84)
urine toxicology (pos/neg)	-	13/3
<i>Amphetamine</i>		
grams/week	-	0.04 (0.12)
years of use	-	1.90 (3.96)
last consumption (days)	-	60.00 (31.61) (n=3)
cumulative dose (grams)	0.03 (0.10)	14.92 (32.86)
hair sample (pg/mg)	-	0.63 (2.50)
<i>GHB</i>		
cumulative dose (pipettes)	-	1.47 (3.38)
<i>Hallucinogenes</i>		
cumulative dose (times)	0.19 (0.54)	13.72 (29.31)
<i>Alcohol</i>		
grams/week	102.42 (159.44)	262.97 (577.14)
years of use	12.75 (9.19)	14.26 (9.01)
<i>Nicotine</i>		
cigarettes per day	4.67 (7.78)	10.88 (11.53)
years of use	5.69 (5.57)	11.16 (9.99)

Means and standard deviation of means in parenthesis

Consumption per week, duration of use, and cumulative dose are averaged within the total group. Last consumption is averaged only for persons who used the drug in the last 6 months. In this case, sample size (n) is shown.



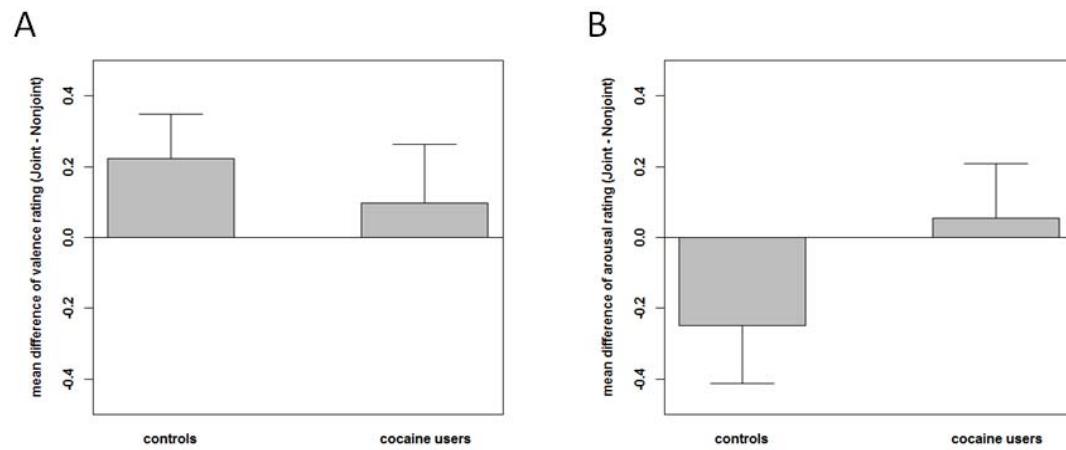
**Figure S2.** Mean arousal ratings for self, other and object condition trials in controls (n=63) and cocaine users (n=80) in study I. All conditions differed significantly from each other (all  $p < 0.01$ ).

**Table S3** Results for errors, completed trials and reaction times in study I

	Controls		Cocaine users		Main effect group			Interaction group*condition		
	Joint	Nonjoint	Joint	Nonjoint	F	df/dferr	p	F	df/dferr	p
Mean errors <sup>a</sup>	0.40	1.40	0.69	1.33	0.13	1/141	0.72	0.57	1/141	0.45
Mean completed trials	4.65	4.52	4.55	4.37	1.18	1/141	0.28	0.37	1/141	0.55
Mean reaction times <sup>b</sup>	1057.31	1274.74	1128.35	1334.68	0.85	1/134	0.36	2.90	1/134	0.09

<sup>a</sup>Errors only for other and object condition<sup>b</sup>Reaction times only for successful trials, only for other and object condition

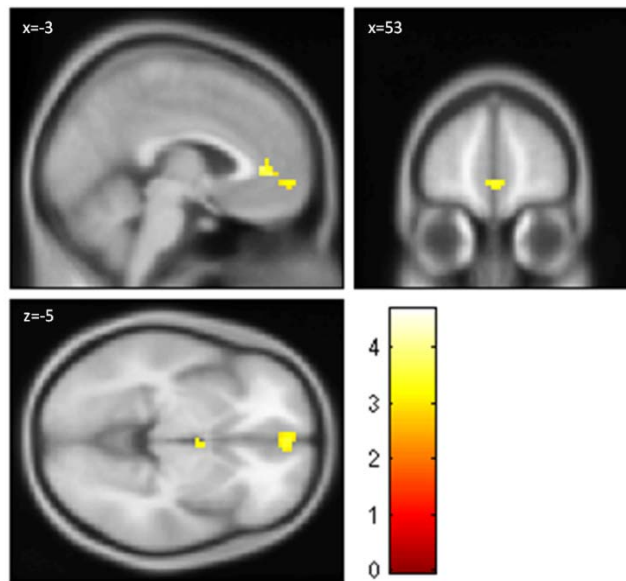




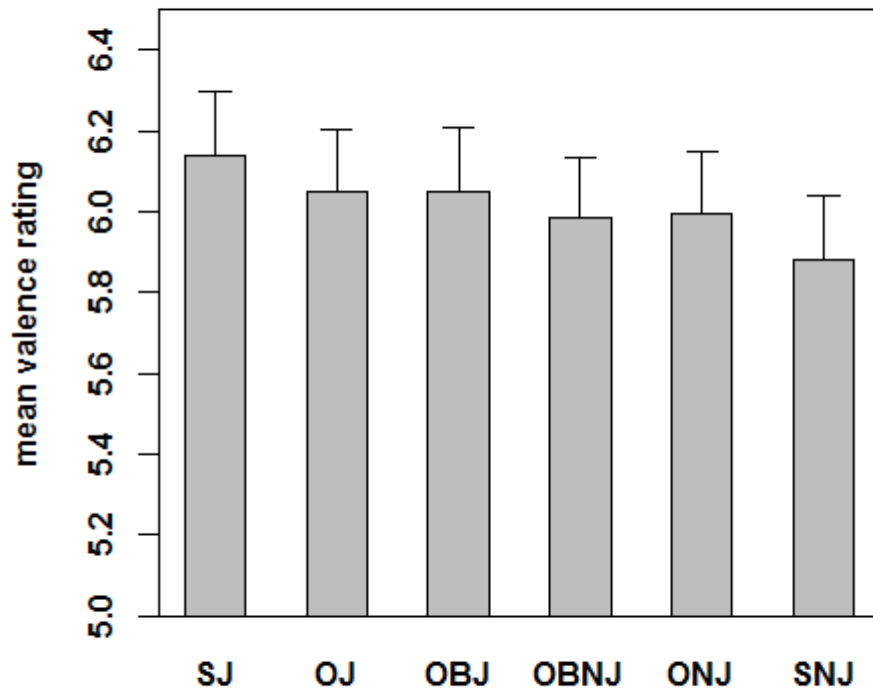
**Figure S3** – Mean difference in valence ratings (A) and mean difference in arousal ratings (B) of joint vs. nonjoint attention trials for controls (n=16) and cocaine users (n=16) in study II. Error bars refer to SEM.

**Table S4** Region of interest analysis of self-initiated joint attention > self-initiated nonjoint attention in study II.

	x	y	z	k	T
<i>Controls only</i>					
Medial PFC	0	44	13	22	3.40
Medial OFC	-3	53	-5	22	3.09
Posterior Cingulate Cortex	-9	-28	28	17	3.71
<i>Controls &gt; Cocaine users</i>					
Medial OFC	-6	56	-5	8	2.75
Statistical threshold: $p < 0.05$ (FWE corrected)					



**Figure S4** – Neural correlates of the contrast self-initiated joint attention > self-initiated nonjoint attention in controls (n=16) (uncorrected  $p < 0.005$ ) (study II).



**Figure S5** – Mean valence ratings for self-joint (SJ), other-joint (OJ), object-joint (OBJ), object-nonjoint (OBNJ), other-nonjoint (ONJ), and self-nonjoint (SNJ) conditions in study I (n=143).

## Methods S1: Recruitment and selection

Subjects were recruited by means of advertisements in local newspapers, drug prevention and treatment centers, psychiatric hospitals, online media, and by word of mouth. Participants were considered eligible for the study if they were aged between 18 and 60 years and had sufficient German language skills. All participants had corrected or corrected to normal vision. For study I, 884 potential participants completed an initial telephone screening, whereof 240 subjects participated in the study. Forty-six participants had to be excluded afterwards because of hair analyses revealing illegal drug use not declared in the interviews (e.g., opioids, excessive MDMA use) or lack of cocaine use. Six participants were excluded because they declared not to have believed in the cover story and maybe did not complete the task appropriately. Four participants could not complete the task because of technical malfunction. Further 41 participants were excluded because of matching reasons (age, IQ, education) between groups. Therefore, 143 datasets were included in the analysis. Because of technical problems, pupil size data were available only for 60 controls and 72 cocaine users.

In study II a subpopulation of 20 cocaine users and 24 controls took part in the fMRI experiment. Completion of the task was not possible for two cocaine users and two controls because of technical problems. Two cocaine users and three controls were excluded due to excessive head movement during scanning (>3mm). Further three controls were excluded because of matching reasons (age, verbal IQ, education, and smoking), therefore data of 16 controls and 16 cocaine users were finally analyzed.

## Methods S2: Social gaze task description

Before the task, all participants received standardized instructions. They were told that they would engage in an interactive game with another participant located in another room but because of anonymity constraints they would not be able to meet the other participant in person. Further, they were told they would see male and female anthropomorphic virtual characters on the screen to keep the sex of the other participant concealed. During the game, they would be instructed to either lead or follow the gaze of the virtual character to one of three objects on the screen, or to look at an object previously determined by the computer. Their gaze behavior would be tracked and transferred to the other participant's computer. Likewise, they would be able to see the other participant's gaze behavior, allowing for real-time interaction.

The experiment comprised three conditions: "self", "other", and "object". Each condition was presented in blocks lasting 18 seconds. Each block was preceded by an instruction screen lasting 2s. In each condition, participants were instructed to first establish eye-contact with the other participant. During the self-task, participants had to choose one of the three objects on the screen and gaze at it. Upon fixation the object turned from grey to blue. Participants were instructed to maintain their gaze on the object until the color would change back to grey (after 1500ms). During this time participants were able to peripherally observe the gaze direction of the other participant, who would either follow the gaze (joint attention) or look at another object (nonjoint attention). The reaction of the other participant varied on a block-by-block basis. After that, participants were asked to reinitiate eye-contact, choose a new object and repeat this procedure until the end of the block.

During the other-task, subjects were told that the other participant had to choose one of the objects and they had to react by either looking at the same object (joint attention) or choose another object (nonjoint attention). In the object condition, one of the three objects flashed up. The virtual character always looked at the indicated object, but the participant was instructed to either gaze upon this object (joint attention) or choose another object (nonjoint attention). Analogously to the self condition, the instruction to establish joint or nonjoint attention varied on a block-by-block basis. If participants reacted correctly according to the instructions, the object's color changed from grey to blue, after which participants were instructed to establish eye contact again and the procedure was repeated until the end of the block.

After each block, participants were asked to rate their experienced valence and arousal during the interaction on a 9-point Self-Assessment Manikin (SAM) scale (69) ("How pleasant/arousing did you perceive the interaction?"; 1=very unpleasant/very relaxing, 9=very pleasant/very arousing). The presentation of male and female virtual characters was balanced across conditions. Twelve blocks of 18s (two repetitions of each condition, in each case two times with instructions to establish joint attention and two times with instructions to establish nonjoint attention) were shown in a pseudo-randomized order. Before the experiment, participants completed each condition to familiarize themselves with the task. The stimuli were presented on a 17-inch monitor 60–70cm in front of the participant. The stimuli were presented using Presentation (Version 14.1, Neurobehavioral Systems, Albany, CA).

Study II: For the fMRI study the task was modified. After the instruction screen (2s) only one interaction (establishment of eye-contact, fixation of participant and avatar on the object according to the condition, object turning from grey to blue) per trial was possible, according to a fast event-related design. One trial lasted for 5s. To simplify the task, only two objects appeared on the left and right of the avatar's face. This version of the task comprised the self and other conditions (each with joint and nonjoint trials) and a baseline condition, during which the participant was instructed to look at one of the objects and the avatar closed his eyes after eye contact was established. Each of these 5 conditions was repeated 20 times, resulting in 100 trials in a pseudorandomized order. A fixation cross was presented between trials with a jittered duration of 3s to 7s (mean 5s). Directly before and after scanning, participants completed each condition two times in a pseudorandomized order (resulting in 20 trials), while lying in the scanner. After each of these trials they were asked to rate their experienced valence and arousal on a 9-point SAM scale analogously to study I.

### **Methods S3: Eye-tracking details**

In study I gaze directions were recorded using the Eyelink 1000 system (SR Research Ltd, Canada), an infrared video-based eye-tracker providing a sample rate of 500 Hz and a spatial resolution of 0.05 degrees. Saccades and fixations were detected on-line. The participant's head was stabilized with a chin-rest. Both eyes were monitored. Pupil size was measured with a resolution of 0.001mm referring to pupil diameter. Eye tracking calibration was performed prior to data acquisition. A baseline pupil size measurement was completed directly before the first trial. Periods of blinks were detected using the manufacturer's standard algorithms with standard settings. For pupil size analysis, all samples were baseline corrected. The pupil size data for the eye with the higher number of valid samples was analyzed. Error trials and trials with data drop outs due to blinks were excluded from the analysis. The samples were averaged for each participant over the duration of one trial. Preprocessing of pupil size data was performed with in-house software.

In study II, an MRI compliant Resonance Technology (Los Angeles, USA) eye-tracking system was used to record gaze directions from the right eye. Saccades and fixations were detected on-line. The eye-tracker had a sample rate of 60Hz, and a spatial resolution of <1degree.